Accuracy of Airflow Obstruction Thresholds for Predicting COPD-Related Hospitalization and Mortality Can Simple Diagnostic Thresholds Be Used for a Complex Disease?

Vestbo, Jørgen; Lange, Peter

Published in:
J A M A: The Journal of the American Medical Association

DOI:
10.1001/jama.2019.6584

Publication date:
2019

Document version
Peer reviewed version

Accuracy of Airflow Obstruction Thresholds for Predicting COPD-related Hospitalization and Mortality:

Can simple diagnostic thresholds be used for a complex disease?

Jørgen Vestbo DMSc[1,2] and Peter Lange DMSc[3,4]

1. Division of Infection, Immunity and Respiratory Medicine, University of Manchester, Manchester Academic Health Science Centre, Manchester, UK
2. North West Lung Centre, Manchester University NHS Foundation Trust, Manchester, UK
3. Institute of Public Health, Section of Epidemiology, Copenhagen University, Denmark
4. Medical Department, Respiratory Section, Herlev-Gentofte Hospital, Copenhagen University, Herlev, Denmark.

Correspondence: Professor Jørgen Vestbo
2nd Floor, ERC Building
Wythenshawe Hospital
Southmoor Road
M23 9LT Manchester
UK

Phone: +45 30350317
Mail: jorgen.vestbo@manchester.ac.uk

Word count: 1230

Diagnostic criteria for complex chronic diseases often include a threshold for a biomarker. In the case of chronic obstructive pulmonary disease (COPD) and hypertension, physiological biomarkers are applied. For COPD, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) states that in a symptomatic individual with a relevant exposure (such as smoking), "the presence of a post-bronchodilator $FEV_1/FVC < 0.70$ confirms the presence of persistent airflow limitation and thus of COPD" (1). A decreased ratio between forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC) is an accepted measure of airflow limitation, but debate around the most accurate threshold level has been ongoing for decades (2,3).

In this issue of JAMA, Bhatt et al. (4) showed that the simple fixed ratio of $FEV_1/FVC < 0.7$ for defining airflow obstruction has the same prognostic value regarding COPD-related hospital admissions and mortality as using the lower limit of normal (LLN, defined as the lower 2.5^{th} percentile of a healthy reference group adjusted for age, sex, race, and height) of the ratio as threshold. The authors used pooled data from 24,103 adults (mean age at baseline, 63 years) from four well-characterized US cohorts [Atherosclerosis Risk in Communities Study (ARIC), Cardiovascular Health Study (CHS), Health, Aging and Body Composition Study (HealthABC) and Multi-Ethnic Study of Atherosclerosis (MESA)] to determine the discriminative accuracy of various FEV_1/FVC fixed thresholds for predicting COPD-related events (ie, hospitalization and mortality). The presence of airflow obstruction was defined by FEV_1/FVC less than a range of fixed thresholds (0.75 to 0.65) or the lower-limit-of-normal (LLN), defined by Global Lung Initiative (GLI) reference equations. The optimal fixed FEV_1/FVC threshold, defined by the best discrimination of COPD-related events, was evaluated based on 3793 COPD-related events that occurred over a median follow-up of 15 years. Compared to a covariates-only model (c statistic, 0.680), the $FEV_1/FVC<0.70$ threshold optimized discrimination of COPD-related events (c statistic, 0.760, incremental c

statistic for improved discrimination, 0.079, P<0.0001) and had discrimination that was not significantly different compared with the LLN (c statistic, 0.762, P=0.55 versus c-statistic for FEV_1/FVC <0.70). Compared with the LLN, the fixed threshold of 0.70 demonstrated lower specificity (79% vs 88%), and higher sensitivity (65% vs 50%).

These findings invariably raise the question – why use a spirometry threshold for diagnosing COPD? Breathlessness is frequent in middle-aged and elderly smokers and can have numerous causes. Detecting the presence of airflow limitation makes it likely that the patient's symptoms can be ascribed to lung disease, and a number of studies have documented that even mild fixed airflow limitation can lead to physiological impairment (5). However, as multimorbidity is the rule rather than an exception in patients with COPD, excluding other causes of breathlessness, in particular heart disease, is mandatory (6).

Most clinicians will agree that many patients with COPD are diagnosed too late because spirometry is not routinely performed in symptomatic smokers. It is also clear that with increasing awareness of COPD many symptomatic smokers are labelled as having COPD until eventually a spirometric examination shows the absence of airflow limitation. The limited uptake of spirometry outside the field of respiratory medicine poses a much larger problem than the definition of the exact threshold debated among respiratory specialists. In addition to mis- and under-diagnosis because of the lack of spirometry, misdiagnosis among individuals with airflow limitation documented with spirometry should also be mentioned. For many years, misclassification between COPD and asthma would most often imply that many individuals with COPD were misclassified as having asthma. However, with increasing awareness of COPD, there is now a need to emphasize that not all individuals with airflow limitation have COPD and that, instead, a

substantial number of them have late-onset asthma with important implications regarding the choice of medical treatment.

The use of either a fixed threshold (which is not adjusted for age, sex, race, ore height) or LLN (which is adjusted) has advantages and disadvantages. A fixed threshold will invariably be biased by age. Undoubtedly, LLN for the FEV_1/FVC ratio is a better measure of airflow limitation in general because LLN adjusts for the strong association between increasing age and decreasing FEV_1/FVC ratio in healthy individuals. However, for use as a diagnostic criterion in a symptomatic individual with an exposure history relevant to COPD (most often smoking), this advantage of LLN may not be that important. Other potential limitations to using the FEV_1/FVC criterion could be more important. First, COPD is mainly a disease of the small airways and the lung parenchyma, whereas the FEV_1 is primarily a measure of airflow in central airways. For this reason, the FEV_1/FVC ratio, particularly using a fixed ratio, is an insensitive measure of early disease. In addition, FEV_1/FVC may be only minimally affected in persons with early emphysema, mild emphysema, or both, an important component of COPD and often associated with progressive disease (7,8). Also, with increasing rates of obesity, the influence of body mass index (BMI) on FEV_1/FVC should not be underestimated. Since FEV_1/FVC increases with increasing levels of BMI, COPD may be underdiagnosed when the usual criteria are applied in the obese individuals (9).

Bhatt et al. used data from large US epidemiological studies, and consequently based their analyses on pre-bronchodilator spirometry obtained at study baseline. This approach is common in epidemiological settings but differs from diagnostic criteria as stated in guidelines, in which spirometry following the administration of an inhaled bronchodilator is advocated. This distinction has always caused a dilemma, because virtually all current knowledge of the natural history of COPD has been derived from studies with repeated pre-bronchodilator measurements. It is

uncertain whether the use of pre- rather than post-bronchodilator spirometry may have affected the prognostic value of the cut-points examined by Bhatt et al. However, a Norwegian population study that included use of a bronchodilator indicated that airflow limitation may be over-diagnosed by up to 25% when a pre-bronchodilator, rather than a post-bronchodilator, FEV_1/FVC ratio is used (10). On the other hand, a pragmatic study from the Netherlands comparing different spirometric indices performed in a setting of general practice, reported that a fixed FEV_1/FVC actually performed better than LLN in diagnosing COPD and that there was no difference in diagnostic accuracy when using either pre- or post-bronchodilator FEV_1/FVC (11). There is also uncertainty associated with using only a single FEV_1/FVC measurement for making a diagnosis; as an analogy, it would be unlikely that a clinician would diagnose hypertension based on a single measurement of elevated blood pressure. The FEV_1/FVC can vary substantially around the threshold value of 0.7 (12), and repeated measurements are therefore recommended (1).

Moreover, in an age of precision medicine and hope of pathway-driven treatments, it does not make sense to diagnose a disease based on a simple physiological measurement. Like most other common chronic diseases, COPD is heterogeneous with several different components and likely many different pathways leading to the disease, as illustrated by the different trajectories of FEV_1 leading to COPD (13). In addition, although a better understanding is emerging of the genetics of COPD (14) and the interactions of small airways disease and emphysema, further research is needed to define subsets of COPD based on mechanisms. While waiting, clinicians may be best advised to continue to use an old, simple measurement for this complex disorder. Now, based on the findings reported in the study of Bhatt and colleagues (4), this simple measurement has better evidence backing its prognostic value.

Acknowledgment

JV is supported by the NIHR Manchester Biomedical Research Centre.

Conflicts of Interest

JV reports a grant from Boehringer-Ingelheim and personal fees from GlaxoSmithKline, Chiesi Pharmaceuticals, Boehringer Ingelheim, Novartis, and AstraZeneca, outside of the submitted work. PL reports grants from AstraZeneca and GlaxoSmithKline and personal fees from Boehringer Ingelheim, AstraZeneca, Novartis, and GlaxoSmithKline outside of the submitted work.

References:

1. Vogelmeier CF, Criner GJ, Martinez FJ, et al. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease 2017 Report: GOLD Executive Summary. Eur Respir J 2017; 49: 1700214. Available on https://goldcopd.org/wp-content/uploads/2018/11/GOLD-2019-v1.7-FINAL-14Nov2018-WMS.pdf, last accessed 22 April 2019.
2. Pellegrino R, Brusasco V, Viegi G, et al. Definition of COPD: based on evidence or opinion? Eur Respir J 2008; 31: 681-2.
3. Hoesein FAAM, Zanen P, Lammers J-WJ. Lower limit of normal or FEV_1/FVC <0.70 in diagnosing COPD: An evidence-based review. Respir Med 2011; 105: 907-15.
4. Bhatt SP, Balte PP, Cassano PA, et al. Identifying the optimal fixed threshold for FEV1/FVC to predict COPD-related hospitalization and mortality: NHLBI Pooled Cohorts Study. JAMA 2019; **XX**: **XX-XX**.

5. O'Donnell DE, Neder JA, Elbehairy AF. Physiological impairment in mild COPD. Respirology 2016; 21: 211-23.
6. Lange P, Mogelvang R, Marott JL, Vestbo J, Jensen JS. Cardiovascular morbidity in COPD: A study of the general population. COPD 2010; 7: 5-10.
7. Vestbo J, Edwards LD, Scanlon PD, et al. Change in forced expiratory volume in 1 second over time in COPD. N Engl J Med 2011; 365: 1184-92.
8. Harvey BG, Strulovici-Barel Y, Kaner RJ, Sanders A, Vincent TL, Mezey JG, Crystal RG. Risk of COPD with obstruction in active smokers with normal spirometry and reduced diffusion capacity. Eur Respir J 2015; 46: 1589-97.
9. Çolak Y, Marott JL, Vestbo J, Lange P. Overweight and obesity may lead to under-diagnosis of airflow limitation: Findings from the Copenhagen City Heart Study. COPD 2015; 12: 5-13.
10. Johannessen A, Omenaas ER, Bakke PS, Gulsvik A. Implications of reversibility testing on prevalence and risk factors for chronic obstructive pulmonary disease: a community study. Thorax. 2005; 60: 842-7.
11. Hoesein FAAM, Zanen P, Sachs APE, Verheij TJM, Lammers J-WJ, Broekhuizen BDL. Spirometric thresholds for diagnosing COPD: 0.7 or LLN, pre- or post-dilator values? COPD 2012; 8: 338-43.
12. Aaron SD, Tan WC, Bourbeau J, et al. Diagnostic instability and reversals of chronic obstructive pulmonary disease diagnosis in individuals with mild to moderate airflow obstruction. Am J Respir Crit Care Med 2017; 196: 306-14.
13. Lange P, Celli B, Agustí A, et al. Lung-function trajectories leading to chronic obstructive pulmonary disease. N Engl J Med 2015; 373: 111-22.

14. Sakornsakolpat P, Prokopenko D, Lamontagne M, et al. Genetic landscape of chronic obstructive pulmonary disease identifies heterogeneous cell-type and phenotype associations. Nature Genet 2019; 51: 494-505.